HHS Public Access

Author manuscript

Clin Infect Dis. Author manuscript; available in PMC 2018 May 01.

Published in final edited form as:

Clin Infect Dis. 2017 May 01; 64(9): 1171–1173. doi:10.1093/cid/cix085.

Diagnosing an Infection Control Risk

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If there wasn't cause enough in the alarming increase and plateau at historic highs of *C. difficile* infections (CDI) and associated deaths [1], the recent addition of hospital-onset CDI to the 'pay for performance' program administered by the Center for Medicare & Medicaid Services [2] has further increased the ante on prevention. Yet there is controversy and potential change in two key areas pertaining to the treatment and prevention of CDI that the article by Mawer et al. in this issue of Clinical Infectious Disease traverses [3]. One is the uncertainty surrounding the best method to diagnose CDI; the other is the relative importance of different sources of *C. difficile* transmission in the hospital.

Following the approval of the first nucleic acid amplification tests (NAATs) approximately eight years ago, there has been increasing adoption so that recent data from the National Healthcare Safety Network laboratory survey indicates 65% of hospital laboratories were using a NAAT in the last quarter of 2015 while additional laboratories used an algorithm that incorporated a NAAT (unpublished data). Recent observational studies have called into question whether symptomatic, NAAT+ patients who are toxin enzyme immunoassay (EIA) negative may be only colonized with *C. difficile*, with diarrhea resulting from other causes, suggesting these patients should not be treated [4, 5]. Current recommendations in the United Kingdom are to not treat NAAT+/toxin EIA- patients but consider them colonized and a potential, but heretofore unquantified, infection control risk [3]. Meanwhile in the United States it remains standard practice to both treat and isolate all NAAT+ patients. Multistep algorithms that could potentially provide clinicians with an assessment of both the presence or absence of a toxigenic organism, as well as some sense of the presence or absence of toxin in stool, are used in a minority of U.S. hospitals; even for those settings with such results available, it has not been demonstrated how clinicians should combine results with the clinical context of specific patients to alter management.

Regarding the relative importance of different sources of transmission in the hospital environment, acquisition of *C. difficile* from another (symptomatic) patient with CDI has been long-thought the principal source; current infection control recommendations focus on the containment of transmission from these patients. This paradigm appears now in a state of flux as, at least in hospitals with modern infection control programs, patients commonly isolated and treated for CDI serve as the source for only approximately one third of new

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Disclaimer: The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Both authors report no conflicts of interest.

healthcare-associated cases [6, 7]. Of note, Mawer et al. found as few as 19% of new CDI cases resulted from transmission from another symptomatic patient--they attribute this decline from their previous study [6] to the decline in the hypervirulent ribotype 027 strain [3].

It is in this context of controversy over the best methods for clinical diagnosis and changing importance of different sources of transmission, that the study by Mawer et al. addresses an important question: “To what extent do symptomatic patients with toxigenic *C. difficile* in their stool but no readily detected toxin pose an infection control risk?” The methods employed at two hospitals in England involved screening with an EIA for glutamate dehydrogenase (GDH) followed by toxigenic culture and, depending upon the facility, toxin A/B EIA and/or cell culture cytotoxin neutralization assay (CCNA). The results generated should be roughly generalizable to settings that employ either a GDH/toxin EIA/NAAT or NAAT/toxin EIA algorithm, despite GDH tests being somewhat less sensitive than NAAT for the detection of toxigenic organism and the better performing toxin EIAs being similarly less sensitive than CCNA for detection of toxin. Mawer et al. sort out likely transmission events using whole genome sequencing and single polynucleotide polymorphism (SNP) methods similar to their previous studies [6].

Using abbreviations for toxigenic strain (TS) based upon GDH/toxigenic culture results, and fecal toxin (FT), based upon a mix of CCNA and toxin EIA, patients who were TS+/FT+ were the source of transmission for 10% of subsequent TS+/FT+ cases while those who were TS+/FT− were the source for 3%, and both TS+/FT+ and TS+/FT− patients were implicated as potential sources for 6% of TS+/FT+ cases. Results were similar in considering sources for subsequent TS+/FT+ and TS+/FT− cases combined.

While these results were presented as the contribution of various transmission sources to the total of all healthcare-associated cases, as Mawer et al. point out in their discussion, this does not account for the greater number of TS+/FT+ compared to TS+/FT− potential source patients. Although a more accurate risk calculation may be achieved using a 3-month ‘lead out’ period at the end of the study (similar to the 3 month ‘lead-in’ period used during which no sources were sought for new cases) or possible use of survival analysis (i.e., determining time dependent risk and censoring potential sources at the end of the study period), if one divides the number of cases attributed to both FT+ and FT− sources equally to each source group, one can produce a crude estimate from the available data of the risk that a FT+ or FT − potential source would transmit. Thus the risk that a TS+/FT+ potential source would transmit resulting in a subsequent TS+/FT+ case was 6.8% (34.5/507) or, resulting in either a TS+/FT+ or TS+/FT− case, 9.4% (47.5/507). Similarly, the risk that a TS+/FT− potential source would transmit resulting in a subsequent TS+/FT+ case was 4.7% (16.5/353) or, resulting in either a TS+/FT+ or TS+/FT− case, 7.8% (27.5/353).

What emerges from these calculations, and is also touched on in the discussion by Mawer et al., is that while TS+/FT+ cases are most contagious, TS+/FT− cases are a close second and both groups are much more contagious than asymptomatic carriers. Data on both organism load and skin and environmental contamination appear to support this ordering in the magnitude of contagiousness [8, 9]. However, while asymptomatic carriers (who are much

more numerous) are overall less contagious, there may be some who, either because of ongoing antibiotic exposure or other factors, are similarly contagious as these symptomatic groups. For example, Curry et al. found in asymptomatic *C. difficile* carriers detected among patients at high risk for colonization with vancomycin resistant enterococci that the risk for onward transmission resulting in a TS+/FT+ (detected via CCNA) case was 7% (16/226)[7]. In the recent study by Longtin et al. that demonstrated a 62% reduction in healthcare-associated CDI through the detection and isolation of asymptomatic carriers, reduced antibiotic prescribing in carriers was hypothesized as a potential means through which some of the reduction was effected [10]. While such a reduction in prescribing may be conjectured to decrease progression from carrier status to active CDI, it may also simply maintain carriers at a less contagious state.

Because any estimate of the contagiousness or reproductive potential of different case types or carriers is highly dependent upon the timing and nature of infection control precautions as well as clinical treatments that impact organism load, the heterogeneity of these practices between and across the two study sites is a potential limitation of this study [3]. There was a lower threshold for isolation and clinical testing (i.e. ≥ 1 episode of unexplained diarrhea), as well as use of a potentially more sensitive toxin assay (CCNA) at Leeds. However, at Oxford all patients with > 3 episodes of unexplained diarrhea in 24 hours were immediately begun on empiric oral vancomycin that was discontinued in FT− patients. Given that transmission risk as calculated above (especially from TS+/FT+ patients) was somewhat lower at Oxford (data not shown), this practice may have favorably impacted transmission through an early and more immediate reduction in organism load. Meanwhile, it is not known how often patients at Leeds were treated with vancomycin and how often TS+/FT− patients at either study site remained in (or were placed back into) isolation.

Regardless of these limitations, this study further highlights how properly designed epidemiologic transmission studies that employ whole genome sequencing and SNP analysis can be applied to answer important questions critical to clinical medicine and public health. For now it appears that before instituting broad strategies of active surveillance and isolation of all asymptomatic carriers, hospitals should first work to detect and isolate all or most symptomatic patients who are TS+. Future studies should be designed to determine which asymptomatic patients should be subsequently prioritized for screening and isolation to further reduce in-hospital transmission.

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